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## Cerebral Microinfarcts: The Invisible Lesions

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### SUMMARY

The association between small but still visible lacunar infarcts and cognitive decline has been established by multiple population-based radiological and pathological studies. Microscopic examination of brain sections reveals even smaller but substantially more numerous *microinfarcts*, the focus of the current review. These lesions often result from small vessel pathologies such as arteriolosclerosis or cerebral amyloid angiopathy. They typically go undetected in clinical-radiological correlation studies that rely on conventional structural MRI, though the largest acute microinfarcts may be detectable by diffusion-weighted imaging. Given their high numbers and widespread distribution, microinfarcts may directly disrupt important cognitive networks and thus account for some of the neurologic dysfunction seen in association with lesions visible on conventional MRI such as lacunar infarcts and white matter hyperintensities. Standardized neuropathological assessment criteria and development of non-invasive means of detection during life would be major steps towards understanding the causes and consequences of the otherwise macroscopically invisible microinfarct.

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### CONFLICT OF INTEREST STATEMENT

Dr. Smith reports no conflicts of interest. Dr. Schneider reports serving as a consultant to AVID Radiopharmaceuticals, and serving on advisory boards to Eli Lilly and Company and GE Healthcare. Dr. Wardlaw reports no conflicts of interest. Dr. Greenberg reports no conflicts of interest.

### AUTHOR CONTRIBUTIONS

Dr. Smith performed the literature search, reviewed relevant articles, carried out meta-analysis, wrote the first draft of sections of the manuscript, and made revisions to the manuscript content. Dr. Schneider reviewed relevant articles from the literature search, identified additional relevant articles, wrote the first draft of sections of the manuscript, and made revisions to the manuscript content. Dr. Wardlaw reviewed relevant articles from the literature search, identified additional relevant articles, wrote the first draft of sections of the manuscript, and made revisions to the manuscript content. Dr. Greenberg conceived the project, reviewed relevant articles from the literature search, identified additional relevant articles, and made revisions to the manuscript content.

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## INTRODUCTION

Many neuropathology and neuroimaging studies have shown that asymptomatic cerebrovascular disease is extremely common.. Further, this so-called “silent” pathology accounts for a surprisingly high portion of dementia.<sup>1</sup> Lacunes and white matter lesions (WMLs) in particular have emerged as clear-cut risk factors for dementia in multiple population-based clinical-radiological studies.<sup>2, 3</sup>

While the association between these visible manifestations of cerebral small vessel disease is strong and consistent, the mechanism remains challenging to explain. Are one or two lacunes, for example, truly sufficient to impair cognition as suggested epidemiologically? An important alternative explanation is that those few readily detectable lesions are instead markers for substantially more numerous and widespread infarcts that are not visible to the naked eye. Tiny *microinfarcts* are indeed a well described neuropathologic finding. These lesions are characterized by bona fide tissue infarction, but on a scale that renders them unapparent on gross pathologic examination or conventional structural MR imaging. This review synthesizes current knowledge of the detection, appearance, prevalence, distribution, and functional impact of microinfarcts along with recommended areas for future investigation. Although microinfarcts represent just one in a spectrum of small vessel-associated forms of brain injury (a list that also includes white matter T2-hyperintense lesions and cerebral microbleeds), current data suggest that they may comprise the single most widespread form of brain infarction and thus a major component of the causal pathway between cerebral small disease and cognitive dysfunction.

## SEARCH STRATEGY AND SELECTION CRITERIA

The PubMed database was searched with the Ovid search engine on December 2 2011 using the terms “microinfarct(s)” and “microscopic infarct(s)” as keywords and MeSH headings, and limited to articles including “brain”, “cerebral” or “central nervous system” as keywords or MeSH headings. The search yielded 535 articles. A single author (EES) screened the abstracts and eliminated 438 articles as not relevant; all study authors reviewed the remaining 97 articles. Another 27 relevant articles were identified by consultation with experts and hand searching of the reference lists of the retrieved articles.

## STATISTICAL ANALYSIS

To derive the univariate pooled odds ratio for the relationship between microinfarcts and dementia, we abstracted information on the prevalence of microinfarcts in persons with and without dementia from the studies selected for review (see “Search Strategy and Selection Criteria”). To reduce the risk of bias we only pooled data from community-based studies of all-cause mortality that prospective selected participants during life, without including hospital or clinic-based studies, for example. Univariate odds ratios were graphically displayed as a forest plot and a pooled odds ratio was calculated using the DerSimonian and Laird random effects model.<sup>4</sup> Heterogeneity in the odds ratios across studies was quantified by the I-squared measure<sup>5</sup> and tested using the chi-square test. Statistical analyses were done using Stata version 9.2 (StataCorp, Texas, USA).

## NEUROPATHOLOGY OF MICROINFARCTS

Cerebral microinfarcts are typically defined as sharply delimited microscopic regions of cellular death or tissue necrosis, sometimes with cavitation (that is, a central fluid-filled cavity). The term “microscopic” denotes that these lesions are not visible by gross inspection of the brain but seen by light microscopy (Figure 1).<sup>6–9</sup> The term “infarct” is most commonly used for ischemia-related tissue loss, and indeed the pathologic appearance

of microinfarcts is consistent with that of known ischemic infarctions. The precise pathophysiologic cause or causes of microinfarcts are not entirely defined, however. To be consistent with prior literature, we will nonetheless continue to refer to these lesions as “microinfarcts.”

There are surprisingly few guidelines for the identification of microinfarcts, and many studies provide little information on inclusion or exclusion criteria. The National Institute of Neurologic Disorders and Stroke – Canadian Stroke Network Vascular Cognitive Impairment (NINDS-CSN VCI) Harmonization Standards<sup>6</sup> uses the standard approach defining microinfarcts as lesions “not visible to the naked eye but detected on histologic examination” and further suggest that microinfarcts be differentiated from “incomplete ischemic injury” or subinfarctive lesions, which appear as foci of cell loss or tissue rarefaction with reactive changes but without frank tissue loss. However, this differentiation can be difficult in practice. For example, a tissue section at the periphery of a genuine microinfarct may demonstrate only subinfarctive changes, as cavitated infarcts can be surrounded by gliosis some distance from their nidus.<sup>10</sup> For this reason, some studies are inclusive of these incompletely infarcted lesions and define microinfarcts to include foci of tissue pallor or astrocytosis,<sup>8, 11, 12</sup> whereas others require evidence of frank tissue necrosis or encephalomalacia.<sup>7, 13, 14</sup> Some studies further exclude infarcts that are over 2 mm<sup>14</sup> or 4 mm<sup>12</sup> in diameter; presumably to exclude lesions that should be grossly visible. Another source of variability in microinfarct detection is staining method. Although most studies suggest that microinfarcts are readily identified on routine hematoxylin and eosin (H&E) stain,<sup>7, 11</sup> immunohistochemical staining for markers of tissue injury such as reactive astrocytes<sup>15</sup> or activated microglia<sup>16</sup> may make microinfarcts more recognizable and easier to count.<sup>7</sup> However, the sensitivity and specificity of different staining methods for microinfarcts has not been rigorously studied.

When identified in early stages of their evolution, microinfarcts show the predicted acute ischemic appearance of red neurons (if cortical) and loss of tinctorial staining quality, sometimes with vacuolization from cytotoxic edema. In subacute stages (starting at 3 to 5 days post-infarct), the lesions demonstrate an influx of macrophages that often clearly demarcate the central region of the infarct from surrounding tissue. At approximately 10 days this is followed by a surrounding gemistocytic astrocytosis and fading of the dying neurons. Chronic lesions typically show cavitation with few remaining central macrophages and a surrounding fibrillary gliosis. However, chronic microinfarcts can also appear as a linear “scar” with acellularity and fibrillary gliosis but little or no cavitation, causing invagination of the pial surface and puckering of the surrounding tissue when in the cortex, or if numerous, creating a cortical appearance of “granular atrophy”.<sup>17</sup> It is important to note that like other foci of tissue necrosis, microinfarcts can have distant tissue effects such as Wallerian, retrograde, or transynaptic degeneration.<sup>7</sup> The combination of local peri-infarct gliosis<sup>10</sup> and distant degeneration may thus make the pathologic impact of microinfarcts more widespread than simply the tissue volume occupied by the microinfarcts themselves.

Typical microinfarct size appears to be quite small. In a study of microscopic lesions containing tissue necrosis, mean diameter of the lesions was approximately 0.2 mm.<sup>18</sup> In another community-based clinical-pathologic study of aging the average size was much larger, 1mm, with a range of 0.2 to 2.9 mm.<sup>19</sup> The small average size highlights the challenges in designing imaging methods for detecting microinfarcts (see later Neuroimaging of Cerebral Microinfarcts).

Microinfarcts are very common in the aging brain. Estimates of the frequency of one or more detectable microinfarcts range from 16% to 46% in unselected elderly persons dying of all causes (Table 1). Microinfarcts were detected in 33% of cognitively normal elderly

dying of all causes in a combined analysis of 4 studies.<sup>20</sup> The heterogeneity in observed prevalence likely arises in part from differences in cohort characteristics such as age and coexisting medical conditions. An additional source of variation is the sampling strategy. Because microinfarcts are very small lesions within a large brain that is typically only sparsely sampled for microscopic pathology, their prevalence is likely to be affected by both the volume and location of examined tissue. Sampling strategy is not necessarily the overriding determinant of microinfarct prevalence, however; for example, a frequency of 19.3% was reported with 38 regions sampled<sup>11</sup> whereas another study found a frequency of 30% with only 9 regions sampled.<sup>21</sup>

Microinfarct burden is often expressed as the number of microinfarcts per number of blocks from specific regions<sup>16</sup> or by semiquantitative estimates across all sampled tissue blocks (e.g. none, one, more than one or more than two).<sup>8, 14, 22</sup> The numbers of microinfarcts detected in these studies are likely vast underestimates of the total brain burden, however, as even systematic tissue sampling methods examine only a tiny fraction of the overall brain volume. Calculations based on the sampling protocol used in reference 21 indicate that observation of 1 or 2 microinfarcts in sampled tissue suggests the likely presence of hundreds of microinfarcts across the total brain volume (Schneider and Greenberg, unpublished data). Although direct measurement of total brain microinfarct burden has not been performed (and may indeed be impractical), these calculations suggest that true number is almost certainly orders of magnitude greater than the total burden of grossly visible lacunar infarcts (typically 1 to 15 per brain).<sup>23</sup>

Determining the distribution of microinfarcts across the brain, like their prevalence and overall burden, is likely influenced by sampling strategy, which varies among studies. A reasonable approach to standardized sampling is the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol for brain sampling with additional sectioning of the anterior (centrum semiovale) and posterior white matter<sup>24</sup> as suggested by the NINDS – CSN VCI Harmonization Standards.<sup>6</sup> Other important areas for sampling may include the border zones of major arterial territories<sup>18, 25, 26</sup> as well as brain regions commonly involved by lacunar infarction, the basal ganglia, thalamus, pons and cerebellum.

Microinfarct location can be classified as cortical or subcortical, a distinction that may be useful for identifying associations with specific diseases. Some studies of AD, for example, report cortical microinfarcts predominantly in brain arterial border zone areas<sup>18, 25, 26</sup> or in motor cortex in the setting of AD with motor impairment.<sup>27</sup> Cortical microinfarcts have also been associated with cerebral amyloid angiopathy (CAA),<sup>16, 26, 28–32</sup> though the relationship may be complicated by CAA-related perivascular hemosiderin deposition and astroglial scarring that can be difficult to distinguish from incomplete microinfarction. Subcortical microinfarcts, particularly in the putamen, have been described in hypertension<sup>33</sup> and hypertensive encephalopathy<sup>34</sup>, and are probably associated with arteriolosclerosis, whereas periventricular microinfarcts have been described in normal pressure hydrocephalus.<sup>35</sup>

## MICROINFARCTS AND SMALL VESSEL BRAIN DISEASE

In using the term “microinfarcts” for these lesions, the underlying supposition is that these lesions are indeed the results of ischemic injury. Several lines of evidence support this inference. As noted above, microinfarcts appear to share the histopathologic structure and progression of macroscopic infarcts. Another suggestive feature is their association with other markers of cerebrovascular disease such as ischemic macroscopic infarcts, leukoencephalopathy, and intracerebral hemorrhages.<sup>7, 21, 36–38</sup> Most notable are the observed associations of microinfarcts with advanced small vessel diseases,<sup>14</sup> including both common age-related pathologies such as arteriolosclerosis and CAA<sup>16, 26, 28–32</sup> and

uncommon hereditary syndromes such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).<sup>39, 40</sup> Microinfarcts commonly coexist with degenerative pathologies such as AD<sup>8, 9, 21, 37, 41</sup> but the number of microinfarcts does not appear to be related to the severity of AD pathology.<sup>19</sup>

Relatively few studies have systematically examined the relationship between microinfarcts and vascular or other epidemiologic risk factors. Hypertension was identified as a risk factor in two prospective cohort studies,<sup>37, 42</sup> though not in another small study.<sup>43</sup> When examined in detail, the association between blood pressure and microinfarcts was seen in those under age 80 but not those 80 and older, and was restricted to higher systolic but not diastolic blood pressure readings.<sup>42</sup> There is a reported association between cerebral microinfarcts and history of coronary artery disease.<sup>37</sup> Two studies have found associations between microinfarcts and advanced age at death.<sup>36</sup> The relationship with gender has been inconsistent.<sup>36, 37</sup>

## NEUROIMAGING OF CEREBRAL MICROINFARCTS

The autopsy-based studies discussed to this point are cross-sectional and therefore limited in their ability to explore the incidence and consequences of microinfarcts. Therefore, there is a need to identify microinfarcts during life in well-characterized clinical populations. The major barrier to this goal is that microinfarcts are, by definition, invisible to the naked eye pathologically and thus likely invisible to conventional structural MRI as well. This quality puts microinfarcts in a distinct category from other features of cerebral small vessel disease that are readily visible on conventional MRI, such as lacunar infarcts, white matter T2 hyperintensities (WMH), enlarged perivascular spaces, microbleeds, and atrophy.<sup>44</sup>

The paucity of clinical-imaging-pathological correlations<sup>45</sup> means that it is difficult to be certain whether some features or consequences of microinfarction might indeed be detectable on structural MRI. Microinfarcts may, for example, contribute to the overall appearance of WMH,<sup>46</sup> but cannot easily be distinguished from the other pathologies that contribute to this common MRI finding. It is notable that most imaging-pathological comparisons of patients with small vessel disease to date have focused on periventricular and deep white matter rather than cortical lesions,<sup>45, 47</sup> whereas pathological studies of microinfarcts have predominantly sampled the cortex. It is also possible that some of the spherical or ovoid lesions described in recent studies as enlarged perivascular spaces (that is, small CSF containing lesions visible in the white matter and basal ganglia on conventional T2-weighted imaging)<sup>48–50</sup> may actually be microinfarcts.

Given a mean diameter of 0.2 to 1 mm,<sup>18</sup> the size of most microinfarcts is below the lower limit of spatial resolution (approximately 1 mm<sup>3</sup>) for MRI at the conventional (1.5 or 3 Tesla) field strengths used in clinical practice. Lesions smaller than 1 mm will only be visible if the lesional signal is strong enough to be detected despite partial volume averaging with normal tissue also contained in the 1 mm<sup>3</sup> voxel. Therefore, increased spatial resolution will likely be needed for MRI to be able to detect individual microinfarcts and differentiate them from other tiny lesions. Methods to increase the signal to noise ratio, such as higher field strengths, might improve the visual contrast between microinfarction and normal tissue and thus aid detection. A recent study using 7 Tesla post-mortem MRI, where multiple lengthy acquisitions can be done and averaged to reduce noise, demonstrated infarcts in the sub-millimeter range in a brain affected by CADASIL (Figure 2).<sup>51</sup>

During the acute phase, macroscopic infarcts can be sensitively<sup>52</sup> (but imperfectly<sup>53</sup>) detected by MRI diffusion-weighted imaging (DWI).<sup>54</sup> Acute infarcts are visible as hyperintense regions on DWI images or as hypointense regions on apparent diffusion coefficient (ADC) images, reflecting decreased (restricted) diffusion of water protons in the



infarcted tissue. In acute infarction, water molecule diffusion decreases within minutes of the onset of ischemia, then increases as barriers to diffusion, such as cellular membranes, are broken down and scavenged.<sup>55–57</sup> The rate of evolution is more rapid in gray matter than white matter,<sup>58</sup> and may be more rapid for smaller infarcts than larger infarcts and for milder ischemic injuries than more severe. Lesions as small as 1 to 2 mm are detectable on MRI, possibly somewhat enlarged from their pathological dimensions by the “blooming” effects of the strong lesion signal.<sup>59</sup> The size of the smallest infarcts detectable on DWI thus approaches the boundary between what is pathologically considered a microinfarct versus a macroscopic lacunar infarct. As the lesion evolves and ADC increases, the size of the lesion may shrink and either cavitate, take on the appearance of WMH or even be indistinguishable from normal tissue.<sup>60</sup> There is thus only a relatively short time window (perhaps days) in which a microinfarct might be DWI-detectable.

Despite these substantial temporal and spatial limitations, a surprisingly high rate of incidental acute small infarction is detectable on DWI in patients with small vessel disease such as CAA and CADASIL.<sup>61, 62</sup> In a study of CAA patients, for example, DWI-positive lesions were detected in 12 of 78 (15%) including 5 with 2 lesions (Figure 3).<sup>61</sup> Based on these data and a possibly generous estimated 10-day window in which the DWI lesions might remain visible, the authors calculated that the average CAA patient may have 8 incident DWI-detectable small infarcts per year.<sup>61</sup> Similarly, incidental small DWI-positive lesions were detected in 16 to 19% of patients with acute lacunar stroke in 2 studies<sup>63, 64</sup> and 13 to 31% of patients with acute intracerebral hemorrhage,<sup>65–67</sup> with one study finding that DWI-positive lesions were more frequent in the patients with CAA.<sup>66</sup>

The apparent association of incidental DWI-positive lesions with advanced small vessel diseases as well as the absence of definite embolic sources in most cases<sup>68</sup> support the possibility that some of these lesions represent may acute microinfarction. However, it is not known with certainty whether these DWI-positive neuroimaging lesions correspond pathologically to acute microinfarcts, and direct DWI-pathological correlation therefore remains an important goal for future investigation.

The brief time window for acute infarct detection by DWI imposes substantial limitations to assessing the cumulative impact of ongoing acute small infarction. Detection of chronic microinfarcts would be extremely useful, but faces technical challenges in spatial resolution and in discrimination from other types of very small chronic lesions like focal WMH and enlarged perivascular spaces.<sup>48–50</sup> Possible approaches to improved microinfarct detection are discussed below under Areas for Future Investigation.

## MICROINFARCTS, COGNITIVE IMPAIRMENT, AND NEUROLOGIC DYSFUNCTION

Data from the autopsy- and DWI-based studies described above suggest that though individually small, microinfarcts may be quite numerous and thus capable of causing clinical symptoms. The clinical syndrome most clearly related to microinfarction is cognitive dysfunction.

Microinfarcts are frequently seen in autopsies of persons with vascular dementia or mixed dementia.<sup>7, 28, 43, 69–73</sup> However, determining whether microinfarcts contribute to the risk of dementia is challenging, for two reasons. First, the frequency of microinfarcts is also relatively high in brains of non-demented persons.<sup>72–74</sup> Second, other vascular pathologies—such as macroinfarcts, WMLs or CAA—are often seen along with microinfarcts in the same brains. For these reasons, large samples including both demented and non-demented

persons with statistical modeling to control for the presence of other pathologies are needed to determine the independent effect of microinfarcts on the risk of cognitive impairment..

A series of hospital-based autopsy studies from a single center suggests that microinfarcts are indeed an independent predictor of cognitive dysfunction when simultaneously accounting for other pathologies, including macroinfarcts. In these studies microinfarcts were independently associated with increased odds of worse cognitive function in selected populations with low<sup>75, 76</sup> or high<sup>77</sup> levels of neurofibrillary tangle pathology, and with<sup>76, 77</sup> or without<sup>75</sup> accompanying macroinfarcts (including lacunes). In their most inclusive cohort containing all levels of neurofibrillary tangle pathology and macroscopic infarcts, the cortical microinfarct score (range, 0–3) was independently associated with a 1.21-fold increase in the odds of antemortem dementia per additional point on the score (95% confidence interval 1.12–1.31,  $P < 0.001$ ).<sup>77</sup> In patients with low or intermediate levels of neurofibrillary tangle pathology (defined as Braak stage <III), cortical microinfarcts were the single pathology that explained the most variation in Clinical Dementia Rating (CDR) scale score even when simultaneously controlling for macroinfarcts and lacunes.<sup>76, 78, 79</sup> The authors suggested that cortical microinfarcts may make the clinical expression of dementia more likely when there are intermediate levels of AD pathology present, as has also been observed with macroscopic lacunar infarcts.<sup>80, 81</sup> Limitations of these studies is that cases were selected from a geriatric and psychiatric hospital and thus may not be representative of the general population.

Most recently, the cognitive impact of microinfarcts has been investigated by several autopsy studies based on prospective cohorts that are more representative of the community than hospital- or clinic-based series. These studies recruited participants from the community, including non-impaired persons, and prospectively followed them with cognitive testing until death. After death, brain autopsies were conducted to identify the neuropathologies associated with cognitive impairment or dementia (Table 1).<sup>8, 11, 19, 21, 27, 37, 82</sup> The prevalence of microinfarcts ranged from 18% to 30% in 5 of the 7 studies. The other two studies reported higher prevalences of microinfarcts (>40%); in one, the mean age at death was relatively high (more than 90 years),<sup>82</sup> while in the other, the reasons for a higher prevalence of microinfarcts were unclear but could possibly be related to the sampling strategy.<sup>8</sup> Four of the 7 studies found a higher prevalence of microinfarcts in persons with dementia compared to persons without dementia (30 to 64% versus 12 to 38%),<sup>8, 11, 37, 82</sup> and 5 of the 7 studies found an independent association between microinfarcts and dementia in multivariable-adjusted analyses.<sup>8, 11, 19, 37, 82</sup> Microinfarcts were not only common in clinically-diagnosed vascular dementia (18/25, 75%) or mixed dementia (4/4, 100%) but also common in probable AD dementia (32/76, 44%).<sup>82</sup> Pooling the 7 studies, the prevalence of microinfarcts was nearly twice as high in persons who died with dementia (280/488, 57%) than those who died without dementia (208/673, 31%) (Figure 4).

In most cases microinfarcts co-exist with other pathologies, and are infrequently the sole neuropathology in cognitively impaired persons. In two studies, only 13/118 (11%)<sup>11</sup> and 3/179 (2%)<sup>22</sup> of demented persons were found to have microinfarcts as the sole potential cause of dementia. About half of patients with microinfarcts also had grossly visible macroinfarcts, particularly lacunar infarcts; conversely, about half of patients with macroinfarcts had accompanying microinfarcts.<sup>19, 22</sup>

To disentangle the relative contribution of these correlated pathologies—microinfarction and macroinfarction—in the same set of brains, multivariable statistical modeling can be employed. When controlling for the presence of larger infarcts including lacunes, microinfarcts were independently associated with the risk of dementia in a series of single



center hospital-based studies,<sup>75–77, 79</sup> and in three prospective community-based studies.<sup>11, 19, 37</sup> In several of these studies larger infarcts were also associated with the risk of dementia,<sup>19, 37, 76, 77</sup> while in others only microinfarcts, but not larger infarcts, were associated with dementia in the fully adjusted models.<sup>11, 75, 79</sup> In another study microinfarcts, but not larger infarcts, were associated with dementia in univariate analysis.<sup>8</sup> Conversely, only a single study found the opposite—that larger (macroscopic) infarcts, but not microscopic infarcts, were associated with dementia in univariate and multivariable-adjusted analyses.<sup>21</sup> Finally, a single study found that neither microinfarcts nor larger infarcts were associated with dementia when controlling for each other.<sup>27</sup> The preponderance of the evidence therefore suggests that while both microinfarcts and lacunar infarcts may increase the risk of dementia, it is the smaller but more numerous microinfarcts that may be the relatively stronger contributor. More, larger studies with careful pathological assessment are needed to clarify the clinical relevance of microinfarcts compared to the entire spectrum of abnormalities due to small vessel disease, including white matter lesions, microbleeds and ischemic lesions.

There are few data on the prevalence of microinfarcts in persons with mild cognitive impairment (MCI) rather than dementia. One study found an intermediate prevalence of microinfarcts in persons with CDR greater than 0 but no dementia (26/47, 44%) compared to persons who were cognitively normal (25/88, 28%) or demented (47/74, 64%),<sup>8</sup> while another study found no differences between cognitively normal and MCI (normal: 41/170, 24%; MCI 28/134, 20.9%; AD dementia 57/179, 31.8%).<sup>22</sup>

It is reasonable to surmise that the clinical impact of microinfarcts is determined by location as well as number, but this aspect has not been extensively studied. Two studies suggest that cortical microinfarcts may be more closely associated with dementia than subcortical microinfarcts,<sup>19, 37</sup> while another found that both cortical and basal ganglia or thalamic infarcts independently contributed to likelihood of dementia.<sup>11</sup>

The relationship between microinfarcts and neuropsychological test performance has been investigated in a prospective community-based autopsy study.<sup>19</sup> Microinfarcts were associated with episodic memory, semantic memory and visual perceptual speed, but not working memory or visuospatial function, in models controlling for age, sex, education, macroinfarcts, AD pathology and Lewy bodies.<sup>19</sup> Cortical microinfarcts but not subcortical microinfarcts were associated with poor cognitive performance.<sup>19</sup> Microinfarcts were associated with age-related cognitive decline but not the more rapid terminal cognitive decline preceding death.<sup>83</sup>

There is limited information on the relationship between microinfarcts and clinical findings other than cognitive dysfunction. Gait impairment has been linked to microinfarcts in a small number of cases,<sup>69, 84</sup> and a large community-based autopsy study showed that multiple microinfarcts were associated with Parkinsonism after controlling for macroinfarcts and other neuropathologies.<sup>85</sup> Microinfarcts are more prevalent in patients with Parkinson's disease or Lewy body disease compared to healthy controls.<sup>86</sup> Reports on associations with depression are inconsistent. Two studies from the same group failed to find an association between microinfarcts and depression<sup>87</sup> or post-stroke depression,<sup>88</sup> while another smaller study of patients with vascular dementia or Alzheimer's dementia did find an association with depression.<sup>70</sup>

## AREAS FOR FUTURE INVESTIGATION

There are many important directions for future studies that could move the field in the direction of new treatment approaches for preventing microinfarct-related neurologic dysfunction. Some salient possibilities are listed below.

### Develop standardized neuropathologic methods

A standardized approach to the detection, diagnosis, and classification of microinfarcts would allow valid comparisons across populations and research groups, and potentially provide clues to microinfarct pathophysiology. Therefore, development of new consensus standards should be a priority. The standardized method would need to include specific guidelines on which brain regions should be sampled, how tissue should be stained, and how identified lesions should be classified. General guidelines provided by the NINDS – CSN VCI Harmonization Standards<sup>6</sup> provide a reasonable starting point for standard blocking protocols (to include the traditional CERAD regions<sup>24</sup> plus sections of the anterior and posterior white matter<sup>43, 71, 86</sup>); in addition we suggest that basal ganglia, thalamus, pons, cerebellum, occipital cortex, periventricular, arterial borderzone<sup>25–27</sup> and motor regions<sup>27</sup> should be sampled as well. Microinfarct load in both cortical and subcortical brain regions should be recorded. With regard to staining methods, H&E appears to be a good technique for identifying microinfarcts, but with unclear sensitivity and specificity relative to immunohistochemical methods. Given that non-infarct pathologies may result in the clustering of reactive astrocytes or microglia, one may hypothesize that immunohistochemical markers for inflammation or injury may increase sensitivity but decrease specificity for microinfarct detection, suggesting they should be used as an adjunctive but not primary measure at present. Finally, the major outstanding question for microinfarct classification is how to categorize milder injuries without clear cavitation, including the distinct foci of tissue pallor or gliosis that can occur with small vessel disease. Though sometimes referred to as incomplete ischemic injury or subinfarctive injury, there are no detailed standardized definitions or gradations of these injuries, and their relationship with complete microinfarcts is not well established. In the absence of a better understanding of the relationship between “complete” and “incomplete” lesions, it seems reasonable to record and analyze the two lesions individually. Data collection should also include the presumed age of the microinfarct, since established or cavitated microinfarcts might be better correlates of clinical status than recent microinfarcts representing perimortem rather than ante-mortem events. However, by analogy with lacunar lesions, we should not assume that microinfarcts all cavitate or that those that cavitate do so at the same rate.<sup>60</sup> Finally, total counts of microinfarcts should be collected and reported along with the sampling strategy employed, to determine the total burden of microinfarct pathology.

### Collect data on pathologies and risk factors associated with microinfarcts

Despite the emerging impression that these lesions reflect infarction related to advanced small vessel disease, the precise pathogenesis of microinfarcts is not known. It will thus be important to establish which pathologies, risk factors and medical conditions are associated with microinfarcts in different populations. Potential mechanisms for microinfarction include occlusive vascular disease, embolism, hypoperfusion, and disruptions to the blood brain barrier. Focal injury related to oxidative stress, inflammation or other mechanisms are also possible. Indeed, the pathogenesis of microinfarcts may be the result of more than one mechanism. Unraveling these potential mechanisms could be best accomplished by clinical-imaging correlation studies using an accurate, noninvasive method for microinfarct detection during life (see below). In the absence of such an imaging modality, detailed prospective clinical-pathological correlation studies that collect extensive information on associated clinical risk factors and vascular pathologies remain the most compelling approach.

### Determine the full anatomic extent and physiologic impact of microinfarcts

It will be important to establish the mechanisms by which these very small foci of tissue injury result in impaired neurologic function. As noted above, the finding of even a few microinfarcts in a small volume of sampled brain tissue implies a large global burden of microinfarcts and volume of tissue loss; working this out with precision will require more

detailed information on variations in microinfarct density across various brain regions. An intriguing potential approach to this question is post mortem MRI at high field strength and spatial resolution, which offers the theoretical possibility of imaging microinfarcts throughout the entire brain.<sup>89</sup> There may also be related tissue injuries extending beyond the immediate microinfarct focus. These distant injuries could include regional oxidative stress, inflammation or other tissue changes. Alternatively, microinfarcts may be a surrogate marker of other pathophysiologic disruptions such as disruptions in the blood brain barrier or generalized hypoperfusion. Future studies are needed to estimate microinfarct load, related tissue injuries, and the potential roles of inflammation, oxidative stress or blood brain barrier disruptions in promoting brain dysfunction.

### **Identify noninvasive methods for detection of microinfarcts in life**

Establishing accurate means of identifying microinfarcts during life would represent perhaps the greatest step towards elucidating the causes and effects of these lesions. Enhanced detection on MRI could be enabled by higher field strengths<sup>51, 90</sup> and higher spatial resolution, although trade-offs in increased scan acquisition time may make current research approaches challenging for even the most cooperative patients.

Given the technical challenges in identifying individual microinfarcts, a potentially fruitful alternative approach is to infer their presence by identifying patterns of associated lesions. MRI-defined cerebral small vessel disease is associated with increased vascular permeability on MRI,<sup>91</sup> and retinal microvascular abnormalities,<sup>92, 93</sup> but it is not currently known whether these abnormalities are also specifically associated with microinfarction. Other consequences of microinfarction could include regional or global brain atrophy, or subtle alterations in white matter water proton diffusivity or fractional anisotropy detectable using diffusion-tensor imaging.<sup>94</sup> Some small MRI lesions currently considered to be enlarged perivascular spaces might actually represent visible microinfarcts.

### **Incorporate incident microinfarcts as a neuroimaging marker in clinical studies and trials**

Current MRI DWI sequences, though limited in spatial and temporal resolution, offer a convenient and readily available method for detecting at least some incident acute microinfarcts in individuals undergoing MRI in observational or interventional studies. New microinfarcts, if at the larger end of the spectrum (greater than 1 mm), may remain visible as focal hyperintensities on T2-weighted images or lesions with signal characteristics similar to enlarged perivascular spaces. Incident microinfarcts, and possibly incident enlarged perivascular space-like lesions, could thus reasonably be incorporated as ancillary markers in studies aimed at preventing progression of small vessel brain disease. This possibility is particularly attractive for vascular conditions such as hypertensive brain disease or advanced CAA,<sup>61</sup> in which the incidence of these lesions may be high enough to allow a treatment-related reduction to be detectable. An important goal for future investigations in this area will be to collect more data on the appearance, location, and associated risk factors for these small, clinically silent DWI lesions, a promising noninvasive approach towards visualizing the “invisible” microinfarct.

## **CONCLUSIONS**

Despite the large number of unanswered questions about cerebral microinfarcts, it is possible to make some preliminary conclusions. Microinfarcts are quite numerous in the aged brain, particularly in individuals with cognitive impairment or underlying small vessel diseases. Nonetheless, they are difficult to detect directly and specifically during life based on current neuroimaging capabilities. However, MRI DWI detects a surprisingly high incidence of acute small infarctions in patients with symptomatic small vessel diseases,

approaching the upper size limit of pathologically-defined microinfarcts. Mounting evidence from clinical-autopsy correlation studies suggest that the numerous foci of tissue loss related to cerebral microinfarcts may play a direct causal role in cognitive impairment, particularly when present in combination with other age-related brain pathologies. Future work should focus on achieving consensus pathological definitions, improving our understanding of the pathogenesis and consequences to brain structure and function, and developing non-invasive means of detection during life.

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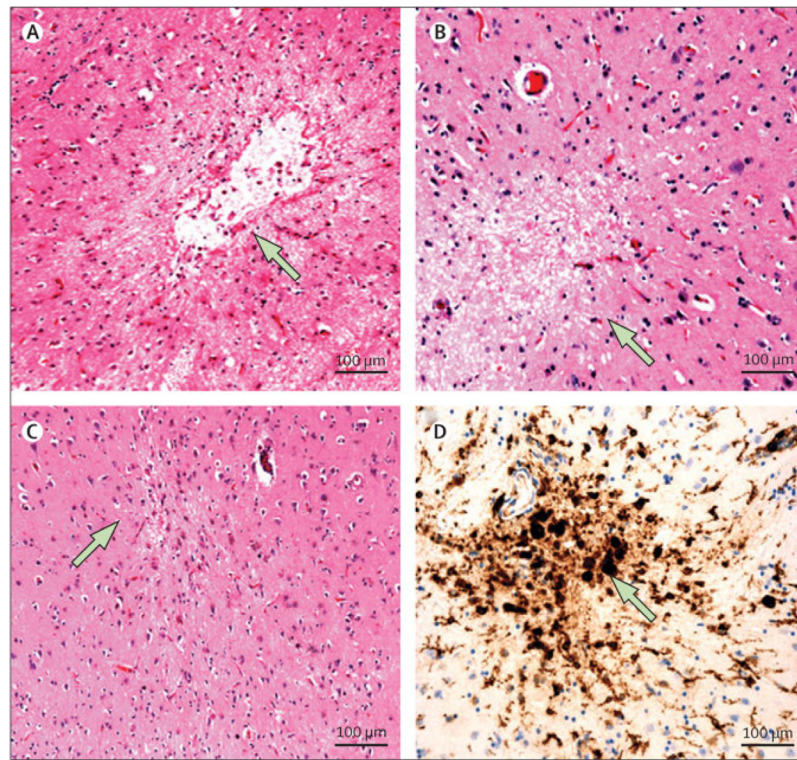
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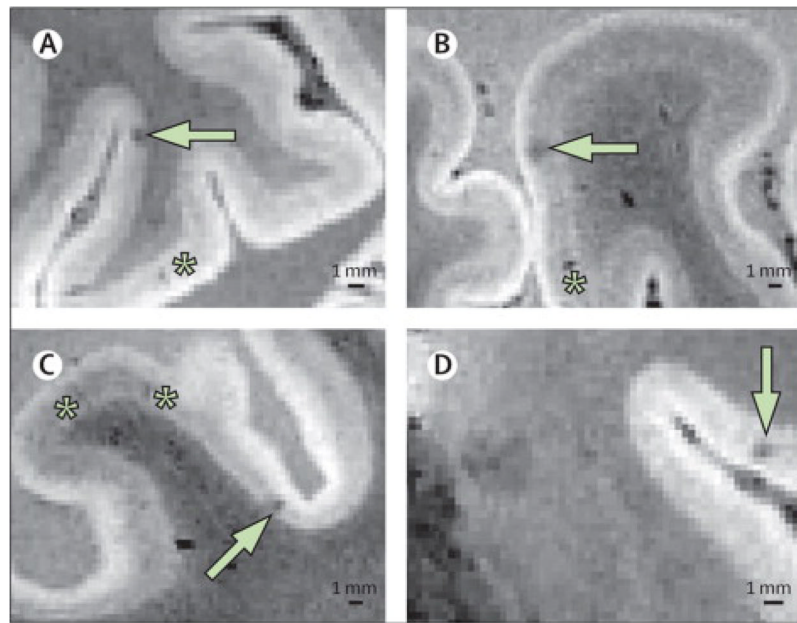
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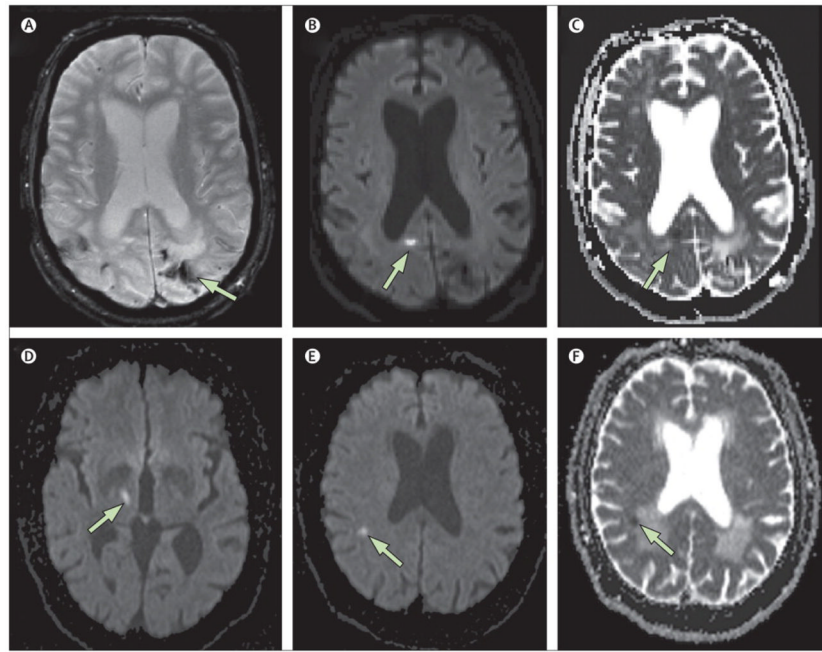
**Figure 1. Microinfarct pathology**

A. Cystic (cavitated) microinfarct (diameter: 600  $\mu\text{m}$ ) in the basal ganglia; original magnification 10x. B. Incomplete microinfarct without cavitation (diameter: 330  $\mu\text{m}$ ) in midfrontal cortex; original magnification 10x. C. Cortical microinfarct with linear scarring (“puckering”) from the middle temporal cortex (diameter 120  $\mu\text{m}$ ); original magnification 10x. D. Immunostatin for major histocompatibility complex II human leukocyte antigen DR3 (MHCII HLA-DR3) expression in activated microglia and macrophages in a microinfarct in the basal ganglia; original magnification 10X (diameter: 320  $\mu\text{m}$ ).



**Figure 2. Intra-cortical Small Infarcts Detected on Post-Mortem High-Field Strength MRI**  
 Examples of pathologically-verified intracortical microinfarcts (white arrows) imaged on post-mortem 7 tesla MRI (voxel size 0.3 mm<sup>3</sup>) of a 53 year old man who died of CADASIL.<sup>51</sup> Asterisks indicate linear hypointensities pathologically proven to be perivascular spaces. The black bar indicates 1 mm. (Figure provided by E. Jouvent).

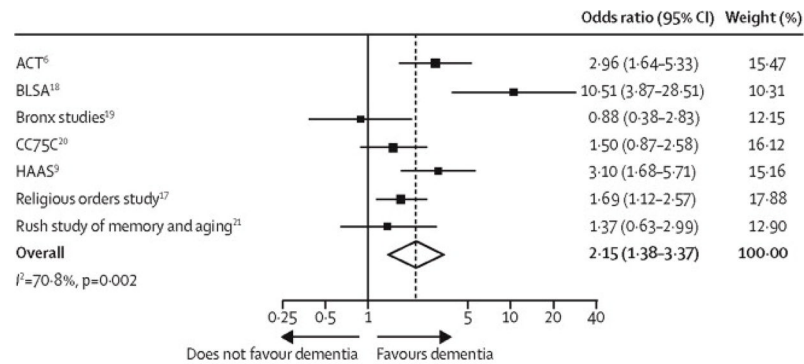




**Figure 3. MRI Diffusion-Weighted Imaging of Small Acute Infarction (Sample)**

Example of small acute areas of restricted diffusion detected incidentally on MRI. Top panels (A–C): A 70 year man with cerebral amyloid angiopathy who underwent MRI as part of a research study. Hemosiderin staining from prior hemorrhages is seen on the T2\*-weighted gradient-recalled echo (GRE) sequence (A). Separate from these prior hemorrhages, an asymptomatic small hyperintensity is seen in the right occipital cortex on the diffusion-weighted image (DWI, panel B) with evidence of restricted diffusion on the apparent diffusion coefficient sequence (ADC, panel C), consistent with an acute small cortical infarct. Bottom panels (D–F): A 67-year old man with an acute symptomatic lacunar infarct in the right thalamus (D, DWI sequence) also demonstrates an asymptomatic small 4.5 mm lesion in the right parietal white matter that is hyperintense on DWI (panel E) with restricted diffusion on ADC (panel F). An asymptomatic simultaneous small vessel infarct was suspected because no proximal source of embolism was identified and there was evidence of coexisting chronic cerebral small vessel disease (note confluent white matter lesions exhibiting increased diffusion in panel F).





**Figure 4. Pooled Odds of Dementia in Persons with Microinfarcts (Unadjusted Analysis)**

The unadjusted odds of dementia were more than doubled in the presence of microinfarcts (odds ratio 2.31, 95% confidence interval 1.40 to 3.82). Significant heterogeneity in the odds across studies ( $p=0.002$ ) may be related to different methods for sampling for microinfarcts. See the legend to Table 1 for an explanation of the study acronyms.

**Table 1**  
Community-based Autopsy Studies of the Relationship Between Microinfarcts and Dementia

Study name	Ref	Autopsy rate	Age at Death (years)	N	Population	Overall	Dementia	No dementia	Multivariable-adjusted Odds Ratio (OR) for Dementia (95% Confidence Interval)
ACT	8	20.1%	Mean 85.0 <sup>1</sup>	221	Washington State USA, randomly selected members of Group Health Cooperative	97/209 (46.4%)	47/74 (63.5%)	50/135 (37.8%)	"Negligible" (reference) <sup>2</sup> 1 or 2 OR 1.13 (0.40–3.04) High 4.80 (1.91–10.26) <sup>3</sup>
BLSA	37	19.3%	Mean 86.9±8.2	179	Baltimore, USA community	39/179 (21.8%)	34/89 <sup>4</sup> (38.2%)	5/90 <sup>4</sup> (5.6%)	6.0 (2.1–17) <sup>5</sup>
Bronx Studies	27	NR	Mean 84.4±9.6	190	Bronx, USA community including nursing homes	30/190 (15.8%)	20/131 <sup>4</sup> (15.3%)	10/59 <sup>4</sup> (16.9%)	0.6 (0.2–1.9) <sup>6</sup>
CC75C Study	82	NR	Median 90.7 (IQR 88.0–93.4)	213	Cambridge, UK, community through general practices	103/213 (48.4%)	60/113 (56%)	43/100 (43%)	2.2 (1.0–5.1) <sup>7</sup>
HAAS	11	22.3%	Mean 84.9	285	Honolulu, USA Japanese-American men	55/285 (19.3%)	35/118 (29.7%)	20/167 (12.0%)	Negligible (reference) Intermediate OR 2.36 (0.87–6.41) High 4.59 (2.07–10.19) <sup>8</sup>
Religious Orders Study	19	94%	Mean 86.5±7.0	425	Older Catholic clergy from multiple U.S. centers	129/425 (30.4%)	70/192 (36.5%)	59/233 (25.3%)	1.77 (1.07–2.92) <sup>9</sup>
Rush Study of Memory and Aging	21	81.1%	Mean 87.9±5.6	148	Chicago, USA community mostly from retirement/seniors housing	35/148 (23.6%)	14/51 (27.4%)	21/97 (21.6%)	0.71 (0.26–1.97) <sup>10</sup>

ACT, Adult Changes in Thought Study; BLSA, Baltimore Longitudinal Study of Aging; Bronx Aging Study (n=54), Albert Einstein College of Medicine Teaching Nursing Home Study (n=99), Einstein Aging Study (n=14), and community volunteers (n=23); CC75C, Cambridge City over-75s Cohort Study; HAAS, Honolulu-Asia Aging Study; Rush Study, Rush Memory and Aging Project. Ref, reference; NR, not reported; IQR, interquartile range.

<sup>1</sup> Estimated from data tabulated by age strata.

<sup>2</sup> "Negligible" indicates 2 or fewer microinfarcts in the cerebral cortex and 2 or fewer microinfarcts in the basal ganglia and thalamus; see reference 9 for details.

<sup>3</sup> Including only patients with dementia (n=89) to patients with normal cognition (n=75), excluding patients with cognitive impairment no dementia (n=47). Adjusted for age, sex, education, and apolipoprotein E e4 genotype.

<sup>4</sup> Percentages of microinfarcts in persons with and without dementia were provided by the authors on request.

<sup>5</sup> Adjusted for age, sex and number of hemispheric macroscopic infarcts.

<sup>6</sup> Adjusted for age, sex, recruitment group, interval from last evaluation to death, macroscopic infarcts, ischemic leukoencephalopathy, Braak NFT stage, and cortical Lewy bodies.

<sup>7</sup> Adjusted for age, time since last clinical assessment while alive, presence of Lewy bodies, presence of white matter pallor and severity grade of neocortical neuritic plaques, entorhinal neuritic plaques, hippocampal diffuse plaques, neocortical neurofibrillary tangles, cerebral amyloid angiopathy and hippocampal atrophy.

<sup>8</sup> Adjusted for age, education, NP, NFT, Lewy Bodies, and hippocampal sclerosis.

<sup>9</sup> Adjusted for age at death, sex, education, macroscopic infarcts, AD pathology (a summary score including measures of neuritic plaques, diffuse plaques and neurofibrillary tangles) and Lewy bodies.

<sup>10</sup> Adjusted for age, sex, education, AD pathology summary measure, and macroscopic infarcts.